

# Significance of Alpha-fetoprotein Levels for Detection of Early Recurrence of Hepatocellular Carcinoma After Hepatic Resection

KEN SHIRABE, MD,\* KENJI TAKENAKA, MD, TOMONOBU GION, MD, MITSUO SHIMADA, MD, YUH FUJIWARA, MD, KEIZO SUGIMACHI, MD, FACS

*Second Department of Surgery, Faculty of Medicine, Kyushu University, Fukuoka, Japan*

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**Background:** The recurrence of hepatocellular carcinoma (HCC) after surgery is common. The present study was conducted in order to clarify the significance of alpha-fetoprotein (AFP) in the detection of the early recurrence of HCC after surgery.

**Methods:** Fifty-eight patients who underwent a curative hepatic resection for HCC and whose preoperative AFP levels were >100 ng/ml, were selected for this study.

**Results:** In 26 cases, the postoperative AFP levels within 3 months after surgery did not decrease to <20 ng/ml (high AFP group). In the other 32 cases, the postoperative AFP levels within 3 months after surgery decreased to <20 ng/ml (low AFP group). No significant difference was observed in clinical or pathological backgrounds. The postoperative disease free rate in the low and high AFP groups was 84.2% and 18.4%, at 1 year, 61.2 and 4.6% at 3 years, respectively. The difference was statistically significant ( $P < 0.01$ ). At the time of recurrence, the AFP levels increased in 25 (96.2%) of the patients who had early recurrence within 1 year after surgery as well as in 11 of 14 (78.5%) who had recurrence >1 year after surgery. The interval from surgery to recurrence significantly correlated with the doubling time of AFP at the time of recurrence in patients with early recurrence (within 1 year after hepatectomy) ( $r = 0.60$ ,  $P < 0.01$ ). In cases in which the preoperative AFP level was >100 ng/ml and the postoperative AFP level did not decrease to <20 ng/ml, early recurrence within 1 year after surgery would thus be strongly suspected.

**Conclusion:** The measurement of the AFP levels after surgery is therefore considered to be important in the follow-up of hepatectomized patients, especially regarding the detection of early recurrence. *J. Surg. Oncol.* 64:143–146. © 1997 Wiley-Liss, Inc.

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**KEY WORDS:** hepatocellular carcinoma; prognostic factor; alpha-fetoprotein; recurrence

\*Correspondence to: Second Department of Surgery, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka, 812, Japan.

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## INTRODUCTION

In patients with hepatocellular carcinoma (HCC), postoperative recurrence is common. Much attention has been focused on finding the predictive factors for recurrence after surgery. Those predictive factors for recurrence that were previously included are portal vein invasion, intrahepatic metastases, tumor size and location, DNA ploidy pattern, and surgical margin from the tumor [1–4]. The preoperative level of AFP has not been considered to be a predictive factor for recurrence in previous studies.

Nevertheless, the measurement of AFP is still useful in the detection of recurrence [5]. In order to detect postoperative recurrence in a timely fashion, preferably within 3 months after surgery, we examined the decline in the AFP levels after surgery and also discuss the significance of AFP in the detection of early recurrence.

## MATERIALS AND METHODS

### Patients

From May 1985 to April 1994, 280 patients underwent curative resection for HCC in the Second Department of Surgery, Kyushu University. The preoperative levels of AFP were no more than 20 ng/ml in 141 (50.4%), more than 20 ng/ml to 100 ng/ml in 81 (28.6%), and over 100 ng/ml in 58 (20.7%) of 280 patients. To exclude the effects of hepatic regeneration [6] and/or response to cellular necrosis in chronic active hepatitis [7], 58 patients with HCC whose preoperative AFP levels were >100 ng/ml, were entered into the study. The patients were divided into two groups by whether the postoperative AFP levels were normalized or not. In 26 patients, postoperative AFP levels within 3 months after surgery did not decrease <20 ng/ml (high AFP group). In the other 32 cases, postoperative AFP levels within 3 months after surgery decreased to <20 ng/ml (low AFP group).

### Procedure

Serum AFP levels were determined, as previously described [8]. In our hospital, the normal range of serum AFP level is set at <20 ng/ml. The doubling time of AFP (DTA) was determined by the formula proposed by Schwartz [7] and based on the hypothesis of Collins and Loeffler [8].

$$DTA = \frac{t(\log 2)}{(\log [ATP\ 1] - \log [AFP\ 0])}$$

where the AFP increase from “AFP 0” to “AFP 1” in “t” days.

After the hepatic resection, all patients were regularly examined every month, and the follow-up comprised a clinical examination and a blood chemistry analysis. The serum AFP concentrations were measured before sur-

**TABLE I. Clinical Backgrounds of the Low and High AFP Groups**

Variables <sup>a</sup>	Low AFP group (n = 32)	High AFP group (n = 26)
Age (yr)	57 ± 9	61 ± 9
Sex (male)	23 (71.9%)	23 (88.5%)
AFP (ng/ml)	6710 ± 9597	11228 ± 36390
Alb (g/dl)	3.7 ± 0.3	3.6 ± 0.4
T.bili. (mg/dl)	0.8 ± 0.4	0.8 ± 0.3
GOT (IU/L)	69 ± 63	69 ± 40
GPT (IU/L)	63 ± 34	65 ± 59
ICGR15 (%)	17.0 ± 12.9	19.9 ± 9.7
HBs Ag (+)	12 (37.5%)	4 (15.4%)
Resected weight (g)	301 ± 271	329 ± 361
Operative procedures		
major hepatectomy	9 (28.1%)	5 (19.2%)
minor hepatectomy	23 (71.9%)	21 (80.8%)
TW (mm)	5.3 ± 8.3	6.1 ± 8.3

<sup>a</sup>AFP = preoperative levels of AFP; alb = serum levels of albumin, T. bili. = serum levels of total bilirubin; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; ICGR15 = retention rate of indocyanine green dye at 15 minutes; HBs Ag = hepatitis B surface antigen; major hepatectomy = lobectomy and segmentectomy; minor hepatectomy = subsegmentectomy and local excision; TW = surgical margin from the tumor. No statistical difference was observed between the two groups.

± = standard deviation.

**TABLE II. Pathological Backgrounds of the Low and High AFP Groups**

Variables <sup>a</sup>	Low AFP group (n = 32)	High AFP group (n = 26)
Tumor size (cm)	4.6 ± 3.4*	4.9 ± 3.8*
pvi	9 (28.1%)	14 (53.8%)
im	9 (28.1%)	12 (46.2%)
Histological grade		
well	4 (12.5%)	3 (11.5%)
moderately	28 (87.5%)	22 (84.5%)
poorly	0	1 (4.0%)
Stage		
I	5 (15.6%)	0
II	12 (37.5%)	12 (46.2%)
III	10 (31.2%)	12 (46.2%)
IV-A	5 (15.6%)	2 (7.6%)

<sup>a</sup>pvi = portal vein invasion of cancer cell; im = intrahepatic metastasis of cancer cells.

\*mean ± standard deviation. No statistical difference was observed between the two groups.

gery, 14 days after surgery, and at every visit to our outpatient clinic. Combinations of ultrasonography and computed tomography were performed at 3-month intervals. When recurrence was suspected, the patients were re-admitted and an angiographic evaluation was made.

### Statistical Methods

The disease-free survival rates were calculated by the Kaplan-Meier method [9] and the difference in the dis-

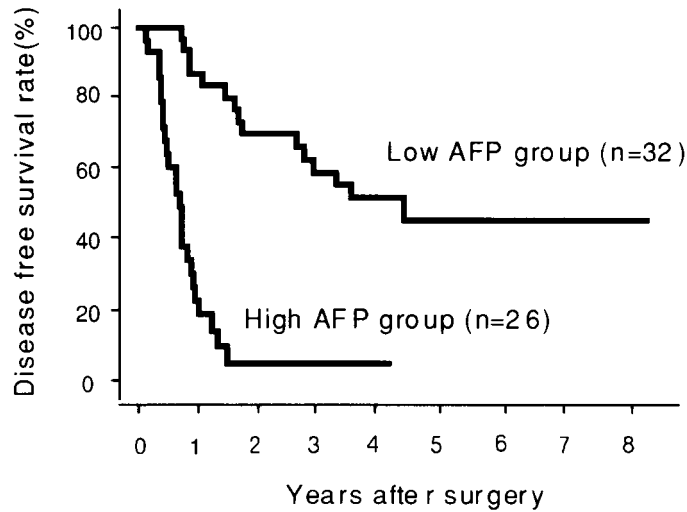


Fig. 1. The disease-free survival of the low and high alpha-fetoprotein (AFP) groups. The disease-free survival in the low and high AFP groups was 84.2% and 18.4% at 1 year and 61.2% and 4.6% at 3 years, respectively. The difference between the two groups was statistically significant at  $P < 0.01$ .

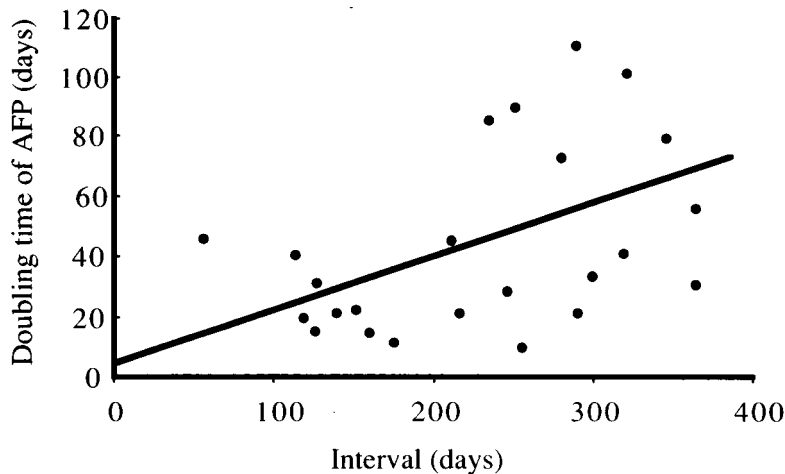


Fig. 2. The interval from surgery to recurrence and the doubling time of alpha-fetoprotein (AFP) at the time of recurrence in 25 patients with early recurrence (within 1 year after surgery). The interval from surgery to recurrence significantly correlated with the doubling time of AFP at the time of surgery ( $r = 0.602$ ,  $P < 0.01$ ).

ease-free survival curves was evaluated by the generalized Wilcoxon test [12]. Both Student's *t*-test, and the Chi-square test were used for the statistical analysis. Significance was defined as a  $P$  value  $< 0.05$ .

## RESULTS

### Clinical and Pathological Backgrounds

The clinical and pathological backgrounds of the two groups was shown in Tables I and II. No statistically significant difference was observed between the two groups regarding clinical background. In the high AFP group, intrahepatic metastasis and portal invasion tended to be more frequent than in the low AFP group, although no statistically significant difference in pathological backgrounds was observed.

### Disease-free Survival Rates

The postoperative disease-free rates in the low and high AFP groups were 84.2% and 18.4%, at 1 year, 61.2% and 4.6% at 3 years, respectively, and the difference was statistically significant ( $P < 0.01$ ) (Fig. 1).

### Postoperative AFP Levels

In 20 cases whose postoperative AFP levels did not decrease to  $< 20$  ng/ml, a steady increase in the AFP levels was observed. All these patients demonstrated early recurrence within 1 year after surgery. In the other six cases, there was no steady increase in the AFP levels and they did not have early recurrence within one year after surgery. At the time of recurrence, the AFP levels

increased in 25 (96.2%) of 26 patients with early recurrence within 1 year after surgery and also in 11 (78.5%) of 14 patients with recurrence later than 1 year after surgery. The interval from surgery to recurrence significantly correlated with the doubling time of AFP at the time of recurrence in patients with early recurrence within 1 year after hepatectomy ( $r = 0.602$ ,  $P < 0.01$ ) (Fig. 2). However, no significant correlation was observed between the interval from operation to recurrence and the doubling time of AFP in the patients with late recurrence later than 1 year after hepatectomy.

## DISCUSSION

In HCC, postoperative recurrence is common and early postoperative recurrence is the main cause of the generally poor long-term prognosis [1–3]. In the present study, the postoperative decrease in the AFP levels was important in the detection of recurrence after a curative resection. Furthermore, the interval from surgery to recurrence correlated significantly with the doubling time of the AFP levels at the time of recurrence in patients with recurrence within 1 year after surgery. These results thus suggested that the occult metastases of HCC, which produced AFP, had already been present at the time of surgery. In this respect, the precise preoperative diagnosis regarding the intrahepatic spreading of HCC is thus considered to be important. The previous data from our clinic demonstrated that HCC measuring  $<5$  mm could not be detected in the preoperative diagnosis. Nevertheless, computed tomography during arterial portography (CTAP) demonstrated the highest rate of detecting in small metastases [13]. Therefore, CTAP should be performed on all preoperative patients and a careful selection of patients also should be done.

In patients whose postoperative AFP level did not decrease to  $<20$  ng/ml and who did not have early recurrence, no steady increase in the AFP level was observed. Although the definite reason as to why the postoperative AFP levels did not decrease to  $<20$  ng/ml remains unknown, the hepatic regeneration after surgery [6] and/or in response to cellular necrosis in chronic active hepatitis might be one possible reason for this phenomenon [7].

Regional prophylactic chemotherapy of the remnant liver has been reported to reduce the recurrence of HCC

after hepatectomy. Nonami et al. [14] reported good results after performing postoperative hepatic arterial chemotherapy on the remnant liver. Takenaka et al. [15] and Izumi et al. [16] also showed that prophylactic lipiodolization reduced the incidence of postoperative recurrence. Nevertheless, adjuvant chemotherapy is often difficult to carry out in patients after undergoing a hepatic resection, with impaired hepatic functions, a reduced performance status, and possibly a suppressed regeneration of the remnant liver [17]. Therefore, the selection of patients demonstrating a higher likelihood of developing early recurrence is necessary to perform adjuvant chemotherapy. In conclusion, a decline in the AFP levels after hepatectomy is considered to be a good predictive factor for the detection of early recurrence.

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